

Prevalence of high serum uric acid is increased in ambulatory subjects with hyperglycemia and dyslipidemia

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A prevalência de hiperuricemia está aumentada em pacientes ambulatoriais com hiperglicemia e dislipidemia

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key words	abstract
Ambulatory subjects	<p>Introduction: Serum uric acid has been considered a marker or an element of the clinical and laboratory alterations in the metabolic syndrome. Objective: to evaluate the association between levels of serum uric acid (UA) and the following laboratory profile: fasting glucose ≥ 100 mg/dl, triglycerides ≥ 150 mg/dl and high density lipoprotein cholesterol (HDL-C) < 50 mg/dl in women and < 40 mg/dl in men. Method: In a cross-sectional survey, blood samples of 4,328 randomized outpatients aged from 20 to 102 years were analyzed. Results: The mean (interquartile range) UA level was higher in men (6.7; 2.4-12.5 mg/dl) and women (5.4; 2.0-12.2 mg/dl) with the laboratorial profile than in those without it (5.9; 0.90-33.8 mg/dl for men and 4.4; 0.8-30.0 mg/dl for women) ($p < 0.0001$). A significant increase in the prevalence of laboratory profile was observed in men (OR = 2.2 mg/dl; 95% CI: 1.2-3.9 mg/dl) and women (OR = 2.2 mg/dl; 95% CI: 1.4-3.5 mg/dl) with hyperuricemia. Conclusion: These results show the association between serum levels of uric acid and metabolic syndrome profile, which corroborates to similar results found in other populations worldwide.</p>
Hyperuricemia	
Hyperglycemia	
Dyslipidemia	

resumo	unitermos
<p>Introdução: O ácido úrico sérico tem sido considerado um marcador ou componente das alterações clínicas e laboratoriais da síndrome metabólica. Objetivo: Avaliar a associação entre o ácido úrico sérico (AU) e o perfil laboratorial composto de glicemia de jejum ≥ 100 mg/dl, triglicérides ≥ 150 mg/dl e colesterol da lipoproteína de alta densidade (HDL-C) < 50 mg/dl nas mulheres e < 40 mg/dl nos homens. Método: Em estudo de corte transversal, amostras de sangue de 4.328 pacientes ambulatoriais não selecionados com idade variando de 20 a 102 anos foram examinadas. Resultados: A mediana (variação interquartil) do AU foi mais elevada nos homens (6,7; 2,4-12,5 mg/dl) e mulheres (5,4; 2-12,2 mg/dl) que apresentaram o perfil laboratorial do que nos que não o apresentaram (5,9; 0,9-33,8 mg/dl para os homens e 4,4; 0,8-30 mg/dl para as mulheres) ($p < 0,0001$). Observou-se aumento significativo na prevalência do perfil laboratorial nos homens (razão de chance [RC] = 2,2 mg/dl; intervalo de confiança [IC] 95%: 1,2-3,9 mg/dl) e mulheres (RC = 2,2 mg/dl; IC 95%: 1,4-3,5 mg/dl) com hiperuricemia. Conclusão: Esses resultados mostram a associação dos níveis séricos do ácido úrico com o perfil laboratorial da síndrome metabólica nesse grupo não selecionado de indivíduos brasileiros atendidos ambulatorialmente, sendo este um achado semelhante ao observado em outras populações estudadas mundialmente.</p>	<p>Pacientes ambulatoriais</p> <p>Hiperuricemia</p> <p>Hiperglicemia</p> <p>Dislipidemia</p>

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Introduction

The investigation of different factors or risk markers is an important clinical task to prevent several chronic diseases, particularly cardiovascular ones. Many of these risks are well defined while others need to be identified. One relevant risk condition to health is the metabolic syndrome (MS), which comprises a cluster of combined clinical and laboratory abnormalities, including increased waist circumference, overweight or obesity, dyslipidemia, systemic arterial hypertension, and glucose intolerance or type II diabetes, all of which reflect insulin resistance and constitute important atherogenic risk factors⁽⁴⁾. Individuals with MS still have increased susceptibility to fatty liver, polycystic ovary, asthma, sleep disturbances, and an increased risk for renal and atherosclerotic cardiovascular disease^(10, 11, 13, 18).

Although the components of MS may suggest its diagnostic when combined, not a single specific marker of the disease exists, and the presence of at least three of those alterations is the requirement for diagnostic of the syndrome^(10, 11). Uric acid (UA) is not considered a criterion for the diagnosis of MS, but some studies have shown an association between high levels of UA and the syndrome in different populations^(3, 7, 15, 17, 21). This is a very important fact because levels of UA can vary in different populations, they are easily measured in a routine fashion, and can help in the identification of the syndrome by investigating for established risk factors. Furthermore, different populations worldwide may have distinctive metabolic peculiarities.

In the present work, we aimed to transversally evaluate, in an unselected sample of ambulatory subjects, the association between UA and a laboratory profile comprising hyperglycemia, hypertriglyceridemia and low HDL-C, which constitute the established laboratory criteria for the diagnostic of MS according to the revised National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATPIII)⁽⁴⁾ revised in 2005⁽¹¹⁾.

Method

Study population

This was a retrospective cross-sectional survey based on a laboratory database of blood examinations from the Clinical Pathology Central Laboratory of the Brasília University Hospital, Brasília, DF, Brazil. The study was conducted between 2002 and 2004 and blood samples of 4,331 ambulatory subjects assisted in this hospital, 20 years

old or older, of whom 1,464 were men (33.8%) and 2,864 were women (66.2%), participated in the survey. Subjects came to the hospital for blood collection and general laboratory examination as part of their routine evaluation for different clinical conditions. For each subject examined only one laboratory examination result was obtained, so that the number of examinations was equal to the number of subjects.

Laboratory data

Individual blood samples were collected in the morning after an overnight fasting period of at least 12 hours. Serum lipid profile including high-density lipoprotein fractions of cholesterol (HDL-C) and triglycerides (TG) was obtained, in addition to serum fasting glucose (FG) and UA.

Elevated serum glucose was defined as fasting glucose ≥ 100 mg/dl, and high HDL-C when serum concentration was > 40 mg/dl in men and > 50 mg/dl in women. Hypertriglyceridemia was characterized as serum TG concentration ≥ 150 mg/dl.

In order to verify the prevalence of the altered laboratory profile in association with the level of UA, the latter was stratified into three levels, having as the cutoff the upper quartile (75th percentile) of the range of values for the whole group of subjects according to gender: ≤ 4.8 , 4.9 to 7.2 and > 7.2 mg/dl for men and ≤ 3.4 , 3.5 to 5.5 and > 5.5 mg/dl for women. Hyperuricemia was defined as UA concentration > 6 mg/dl in men and > 5 mg/dl in women, based on reference values in our population using the specified laboratory method.

Levels of serum TG, glucose, and UA were determined by enzymatic techniques, and the level of HDL-C was measured using the monophasic colorimetric method without precipitation, with a biochemical autoanalyser (Mega® Bayer, Germany)⁽¹⁹⁾.

Statistical analysis

The normality of distribution of laboratory data and UA concentration, discriminated by gender according to different age groups, was initially tested by the Kolmogorov-Smirnov test. Considering that they showed a skewed non-normal distribution, the median (interquartile range) of continuous laboratory variables was compared between age-grouped men and women employing the Kruskal-Wallis test with post-doc Dunns Multiple Comparison Test. The median of serum UA in subjects with and without the altered

laboratory profile was compared in both genders employing the Mann-Whitney test. Proportions of categorical variables were compared using the chi-squared test. The odds ratio (95% CI) was calculated for the association between altered laboratory profile and serum UA stratified into three concentration levels. A statistically significant association or difference between variables was considered when a two-tailed p value was equal to or less than 5% ($p \leq 0.05$), and a weak or trend statistical significance when P value was between 5% and 10% ($0.05 \leq p \leq 0.1$). Processing analysis and graphic design of the data employed the SigmaStat® 3.11/SigmaPlot 9.01 for Windows (Systat Software, Inc., USA, 2004) and the Prism 4 for Windows® (GraphPad Software, Inc., USA, 2005) software packages.

Results

Prevalence of metabolic abnormalities analyzed by gender and age was marginally greater in women (9.04%, 259/2864) than in men (7.17%, 122/1464) ($p = 0.06$). According to gender discriminated by age, prevalence of the altered laboratory profile in the age range of 20-39 was statistically similar in men (4.45%, 15/337) and women (3.86%, 25/646) ($p = 0.49$); in the age range of 40-59 the alterations also occurred similarly in men (8.75%, 55/628) and women (9.78 %, 136/1,390) ($p = 0.24$). Differently, in the age range of 60 years and over, metabolic alterations were observed to be more prevalent in women (11.83%, 98/828) than in men (7.01%, 35/499) ($p < 0.001$). The altered laboratory profile increased directly with age in both genders, except for men older than 60 years (**Figure 1**).

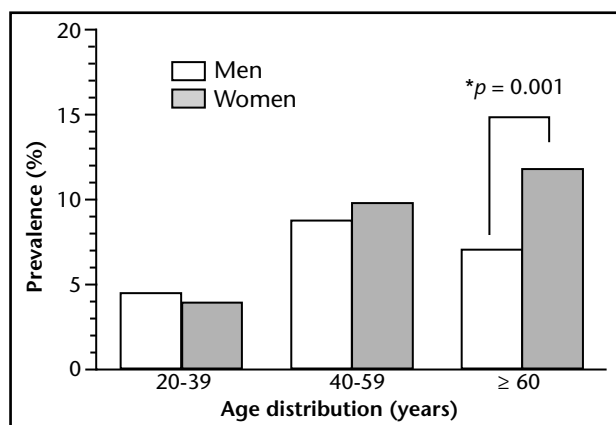


Figure 1 – Prevalence of laboratory profile of the metabolic syndrome in men and women according to age distribution

* p -value for the comparison between men and women in each age range (chi-square test).

Considering the full age range, the median (interquartile range) concentration of UA was observed to be significantly higher in men (6.0; 0.9-33.8 mg/dl) as compared to women (4.4; 0.8-30 mg/dl). Also, UA levels increased with age in both men ($p = 0.003$) and women ($p < 0.0001$). Comparisons between groups of men and women for each age range showed $p < 0.0001$ for each one (**Figure 2**).

In subjects with the laboratory profile the median of UA was higher than in those without it for both genders in the different age ranges ($p = 0.02 \leq 0.0001$) (**Figure 3**). Regarding the association between serum concentration of UA and the altered laboratory profile for the overall age range, a higher median concentration of UA was found in

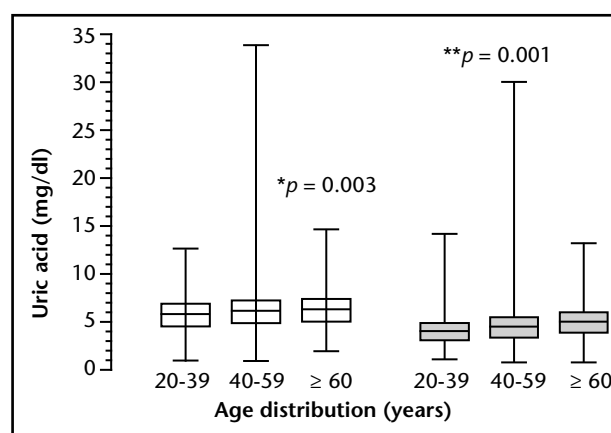


Figure 2 – Median (interquartile range) of serum uric acid in men (left clear boxes) and women (right dark boxes) according to age distribution

* p -value for the comparison between groups of men with the three different age ranges, and ** p -value for the comparison between groups of women with the three different age ranges (Kuskal-Wallis test). Each pair-wised comparison between the groups with the different age ranges, for both men and women, showed a $p < 0.001$; by the post-hoc Dunn's multiple comparison test. Comparisons between the groups of men and women for each age range showed a $p < 0.0001$; (Mann-Whitney test).

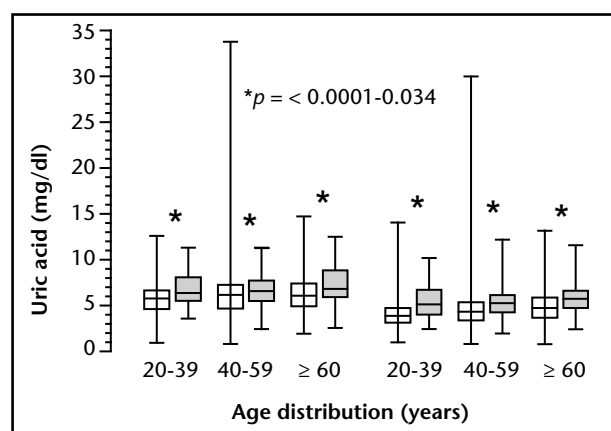


Figure 3 – Serum uric acid in men (left block of comparisons) and women (right block of comparisons) with (dark boxes) and without (white boxes) the laboratory profile of metabolic syndrome, according to age distribution

* p -values for the comparisons between subjects with and without the laboratory profile of MS in each age range (Mann-Whitney test). The data are expressed as median(interquartile range).

men with alterations (6.7; 2.4-12.5 mg/dl) compared with those without it (5.9; 0.90-33.8 mg/dl) ($p < 0.0001$). The same was observed in women with the alterations (5.4; 2-12.2 mg/dl) in relation to those without it (4.4; 0.8-30 mg/dl) ($p < 0.0001$).

Men with serum UA concentration equal to or greater than 7.2 mg/dl (upper quartile) had a 2.21-fold increase in the prevalence of the altered laboratory profile (95% CI, 1.24-3.94), compared with those who had concentrations equal to or less than 4.8 mg/dL (lower quartile). Among women, prevalence of the altered profile was 2.26-fold greater for those with serum UA concentration between 3.5 and 5.5 mg/dl (95% CI, 1.45-3.53), and 5.26-fold greater when serum UA was above 5.5 mg/dl (95% CI, 3.36-8.22), as compared with those who had concentrations of UA equal to or less than 3.4 mg/dl (**Table**).

Discussion

As expected, prevalence of the altered laboratory profile, established as a component of the diagnosis of metabolic syndrome, increased as the population becomes older, especially in women. In the group of women, the subset of those who were 60 years old or older showed the highest prevalence of the metabolic alteration, as compared to men in the same age range. This finding may be justified by a reduced estrogenic protection in the advanced climacteric period, where cardiovascular risk is higher, which is in accordance with other studies^(9, 22, 27). This period in a woman's life is associated with higher levels of LDL-C and lower levels of HDL-C⁽¹⁶⁾. Regardless of this particularity, it is a well-established fact that the defined altered laboratory profile is associated with a higher risk of cardiovascular disease, diabetes mellitus II, microalbuminuria, and renal disease in both genders in any age range^(13, 18).

High levels of LDL cholesterol and triglycerides and low levels of HDL cholesterol increase the cardiovascular risk two fold in healthy adults^(24, 28). The atherogenic risk factor TC/HDL-C ratio had a strong association with coronary heart disease⁽²⁾. Concurrent hypertriglyceridemia and low HDL-C are typical of insulin-resistant subjects and they constitute significant risk factors for cardiovascular disease⁽¹⁾.

But the relevant finding in our study was that, in any age range, both men and women with the laboratory metabolic alteration also showed increased levels of serum UA. Although UA is not included in the criteria for the diagnosis of metabolic syndrome, other studies have also shown a strong association between high serum concentrations of UA and this syndrome or its clinical and/or laboratory components^(3, 7, 15, 17, 21). Recently, Sui *et al.*⁽²⁶⁾, in a prospective study of 8,429 men and 1,260 women (20-82 years old) showed that higher serum UA is a strong and independent predictor of incident metabolic syndrome in men and women.

A possible explanation for the association between increased UA and the metabolic alterations which represent a hyperinsulinemic state would be the stimulant role of insulin on the reabsorption of sodium and urate in the proximal renal tubule^(20, 23). In fact, the degree of insulin tolerance is inversely related to the renal clearance of urate⁽⁵⁾. On the other hand, one independent association of TG and UA was previously demonstrated, and increased TG levels may be associated with decreased UA renal excretion⁽⁸⁾.

Therefore, hyperuricemia may signal the presence of metabolic syndrome and it may also be an additional risk factor for the development of the clinical complications associated with the syndrome. In consequence, it seems important to routinely investigate serum UA level when this syndrome is suspected or when conventional laboratory

Table 1 Odds ratio (95% CI) for the association between the laboratory profile of metabolic syndrome and serum concentration of uric acid in unselected Brazilian ambulatory patients aged 20-102 years

	Men (uric acid concentration, mg/dl)			Women (uric acid concentration, mg/dl)		
	≤ 4.8	4.9-7.2	7.2	≤ 3.4	3.5-5.5	> 5.5
N	373	704	387	731	1.419	714
OR	1	1.3	2.2*	1	2.2**	5.2**
CI	–	0.8-2.4	1.2-3.9	–	1.4-3.5	3.3-8.2

N: number of subjects; OR: odds ratio; CI: confidence interval.

*p = 0.009; **p = 0.001 (chi-square test).

alterations of the syndrome are encountered. On the other hand, when hyperuricemia is detected, the search for conventional markers of the syndrome should always be considered.

Furthermore, evidence suggests a relationship between UA levels and hypertension⁽¹²⁾. Hyperuricemia is also associated with endothelial dysfunction⁽²⁹⁾, which may contribute to increase cardiovascular risk in hypertensive subjects. Moreover, hyperuricemia may be an important risk factor for kidney disease and may lead to the development and faster progression of renal disease^(6, 14, 25).

One limitation of this study was its retrospective design. This type of design and analysis, together with an ambulatory population evaluated for a multiplicity of clinical conditions, inherently increases the likelihood that bias influenced our findings. To this respect, we attempted to minimize bias by analyzing all patients who met the study inclusion criteria. Another limitation was that several confounding variables, in a non-healthy population that attended to the hospital for several reasons, could not be adjusted because the respective data were not obtained. Also, there is a possibility that older patients or patients with metabolic syndrome and arterial hypertension might be using diuretics or other drugs that could eventually increase uric acid levels. However, our objective was to identify an association between UA concentration and the laboratory profile, regardless of other possible comorbidities, and it is

very unlikely that only some subjects in use of drugs can affect the results.

In conclusion, in a cross-sectional survey of a Brazilian unselected ambulatory population, serum concentration of UA was higher in men than in women and increased with age in both genders. In all age ranges and more frequently in women, hyperuricemia stratified in three levels was associated with a clustered laboratory alteration represented by hyperglycemia, hypertriglyceridemia and low HDL-C. In men the frequency of the altered laboratory profile was higher when UA concentration was greater than 7.2 mg/dl. These findings suggest that high levels of UA are a comorbidity and may be a marker or component of an altered metabolic profile represented by the metabolic syndrome. Hyperuricemia should be considered an additional risk factor for different clinical conditions, which demand treatment. To our knowledge, this is the first observation about the association between the clustered laboratory components of metabolic syndrome and hyperuricemia, in an unselected Brazilian population, reproducing similar findings verified in other populations worldwide.

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